

Effect of hepatitis C infection and renal transplantation on survival in end-stage renal disease¹

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Effect of hepatitis C infection and renal transplantation on survival in end-stage renal disease. Hepatitis C virus (HCV) infection is common among patients with end-stage renal disease (ESRD). However, the effect of HCV infection on survival among ESRD patients, and the impact of renal transplantation on the course of HCV infection has not been adequately defined. Sera from patients on the renal transplant waiting list at the New England Organ Bank between November 1986 and June 1990 were tested for anti-HCV using a third generation ELISA. All anti-HCV positive patients and a 1:1 ratio of randomly selected anti-HCV negative patients comprised the study sample. Duration of follow-up was calculated from the date of the first available serum specimen until death, loss to follow-up or December 31, 1995, whichever occurred earlier. Multivariate analysis of risk factors for mortality was performed using a Cox proportional hazards model which included anti-HCV as a time-independent (baseline) variable, transplantation as a time-dependent (follow-up) variable, and independently significant baseline covariates. Anti-HCV was detected in 287 (19%) of 1544 patients in whom sera were available, and 286 anti-HCV negative patients served as controls. Complete information was available in 496 (87%) of these 573 patients. Median follow-up was 73 months (range 1 to 110 months), during which time 302 (61%) patients underwent renal transplantation and 154 (31%) patients died. For anti-HCV positive patients compared to anti-HCV negative patients, the

relative risk of death (and 95% confidence intervals) from all causes was 1.41 (1.01 to 1.97) and due to liver disease or infection was 2.39 (1.28 to 4.48). For patients who underwent transplantation compared to those who remained on dialysis, the relative risk of death from all causes between 0 to 3 months, 3 to 6 months, seven months to four years, and after four years was 4.75 (2.76 to 8.17), 1.76 (0.75 to 4.13), 0.31 (0.18 to 0.54) and 0.84 (0.51 to 1.37), respectively. There was no interaction between the effect of anti-HCV status at baseline and subsequent transplantation ($P = 0.93$), meaning that the association between treatment modality and survival was similar among anti-HCV positive and negative patients, at all intervals after transplantation. We conclude that HCV infection at the time of referral for transplantation is associated with an increased risk of death, irrespective of whether patients remain on dialysis or undergo transplantation. Transplantation has a beneficial rather than adverse effect on long-term survival in anti-HCV positive patients. Hence, anti-HCV positive status alone is not a contraindication for renal transplantation.

Hepatitis C virus (HCV) infection is common among patients with end-stage renal disease (ESRD)[1]. Among 27,086 patients from dialysis centers participating in the National Surveillance of Dialysis Associated Diseases in the United States conducted by the Center for Disease Control and Prevention (CDC), the prevalence of anti-HCV by ELISA2 was 8.1%, with a range of 0 to 51% among centers with at least 40 patients[2]. Likewise, among renal transplant recipients, the prevalence of pre-transplantation anti-HCV ranged from 11% to 49%[3–10]. The effect of HCV infection on patient survival after renal transplantation has been a subject of debate, with some, but not all studies finding an increased risk of death among patients with pre-transplantation anti-HCV[3, 4, 7, 9, 10].

More importantly, the impact of renal transplantation (compared to staying on dialysis) on the course of HCV infection has not been adequately defined. Transplantation is associated with improved long-term survival of patients with ESRD[11]. However, transplantation can also worsen the course of some viral infections[12, 13]. Consequently, transplant physicians have been faced with a dilemma regarding whether anti-HCV positive patients with ESRD should be considered for renal transplantation. With 34,766 patients on the renal transplant waiting list in the U.S. alone[14], the merits of allocating kidneys to anti-HCV positive patients need to be addressed.

We compared the effects of anti-HCV status (positive vs. negative) and treatment modality (dialysis vs. transplantation) on long-term survival in a cohort of patients referred for renal transplantation to centers served by the New England Organ Bank (NEOB).

¹ See Editorial by Goral and Helderman, p. 1420.

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METHODS

Patients

The study sample for this historical cohort study was drawn from all 14 transplant centers in the six New England states served by the NEOB. All patients on the renal transplant waiting list between November 1986 and January 1987 ("prevalent" population) as well as those referred for renal transplantation between February 1987 and June 1990 ("incident" population) were identified from the Tissue Typing Laboratory records of the NEOB. June 1990 was used as the cut-off date because the introduction of anti-HCV testing subsequent to that date could influence referral for renal transplantation. For prevalent patients, the first serum sample available during the period between November 1986 and January 1987 was retrieved for anti-HCV testing. For incident patients, the first serum sample available within six months of referral for transplantation was retrieved for anti-HCV testing. The anti-HCV positive cohort comprised all anti-HCV positive patients. A cohort of anti-HCV negative patients was randomly selected from the prevalent and incident patients at each center in a 1:1 ratio with the anti-HCV positive patients. Recipients of living-related and cadaver donors were included. Recipients from anti-HCV positive donors were not included.

Test for anti-hepatitis C virus antibody

Serum samples, stored at -70°C were retrieved from the NEOB and the Tissue Typing Laboratories at Brigham and Women's Hospital, Massachusetts General Hospital, and Maine Medical Center. Anti-HCV testing was performed using the third generation ELISA (Ortho[®] HCV ELISA 3.0 Test System; Ortho Diagnostics System, Raritan, NJ, USA) which detects antibodies to recombinant HCV antigens (c22, c200, NS5) derived from the nonstructural (NS3, NS4, NS5) and core regions of the viral genome. The assay was performed by Ortho Diagnostics System.

Clinical information

Clinical data were collected from the NEOB records, United Network for Organ Sharing Computer Services, ESRD Networks of New England and New York, databases of the Tissue Typing Laboratories of Brigham and Women's Hospital, Massachusetts General Hospital, and Maine Medical Center, and hospital, transplant office and dialysis unit medical records at the participating centers. Enrollment into the study was defined as the date of the first available serum specimen. Clinical information collected at the time of enrollment included age at onset of renal replacement therapy, gender, race, cause of ESRD, presence of diabetes mellitus, year of initiation of renal replacement therapy (dialysis or transplantation), date of listing for renal transplantation at the NEOB, dialysis modality, history of liver disease and non-A, non-B hepatitis (NANBH), number of blood transfusions, number of previous transplants, blood group, panel reactive antibody (PRA) assay, hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), antibody to cytomegalovirus (anti-CMV), and serum ALT and albumin levels. Serum ALT was considered elevated if it was greater than two and a half times the upper limit of normal. Duration of follow-up was calculated from the enrollment date until death, loss to follow-up or December 31, 1995, whichever occurred earlier.

Statistical analysis

Clinical characteristics were compared between the prevalent and incident cohorts using two-sample tests with two-tailed P values. For continuous variables (age, duration of renal replacement therapy and serum albumin level), Student t -tests were used. For all other variables, χ^2 tests were used.

Univariate and multivariate analysis of risk factors for mortality was performed using a Cox proportional hazards model. Since this was an intention-to-treat analysis, patients who were removed from the waiting list due to illness or complications were analyzed as if they remained on the waiting list from the date of enrollment until end of follow-up. The date of referral for transplantation could be ascertained for the incident group, but not for the prevalent group. Therefore, patient survival was computed from onset of treatment for ESRD. Patients did not contribute to the part of the survival curve during the interval between onset of ESRD and enrollment into the study. Individual patient experience was therefore truncated on the left [15] and censored on the right of the survival curve. Most patients contributed information to the middle part of the survival curve.

The independent variables, anti-HCV status and transplantation, were included in all multivariate models. Anti-HCV status was treated as a time-independent (baseline) variable. Transplantation was treated as a time-dependent (follow-up) variable whose status changed upon transplantation. Almost all patients contributed information to the dialysis group survival curve, but only those who underwent transplantation contributed information to the transplant group survival curve. Patients who underwent transplantation continued to contribute to the transplant curve, irrespective of subsequent graft loss. Several forms of the transplantation variable were examined to determine if its effect changed during follow-up. These included both the simple presence/absence of transplantation as well as linear terms for interval, since transplantation and step functions that allowed the effect to change arbitrarily from year to year and from quarter to quarter within the first year after transplantation. Time-independent (baseline) covariates *a priori* considered for inclusion were age at onset of renal replacement therapy, gender, race (white vs. not white), diabetes mellitus and number of previous transplants. Age and number of previous transplants were treated as linear effects after checking that this formulation was appropriate. In addition, variables listed in Table 2 were included if significant. Two factor interactions between anti-HCV status, transplantation and baseline covariates were also tested.

Variable selection in the multivariate model proceeded as follows using χ^2 likelihood ratio tests with a nominal P value of 0.05 to compare models. (1) All five *a priori* selected baseline covariates, other significant covariates and anti-HCV status were included in a series of models with different parameterizations of the transplantation effect to determine its proper shape. (2) Next, backward stepwise elimination was used to retain only the significant baseline covariates in the final model along with anti-HCV status and transplantation. (3) All two-factor interactions were then examined by comparing the main effects model from step 2 against models with one interaction term added. Interactions were not retained if $P > 0.05$.

Residual diagnostics were performed on these final models. The proportional hazards assumption was checked by computing the Schoenfeld residuals and checking that they exhibited no

Table 1. Characteristics of the study sample^a

Patient population	Sera available ^d	Anti-HCV positive	Anti-HCV negative controls	Total	Complete clinical data available ^e	Follow-up months ^e
Prevalent ^b	394/655 (60%)	139/394 (35%)	122	261	217/261 (84%)	84 (1–110)
Incident ^c	1150/2588 (44%)	148/1150 (13%)	164	312	279/312 (90%)	70 (1–110)
Overall	1544/3243 (48%)	287/1544 (19%)	286	573	496/573 (87%)	73 (1–110)

^a Data for continuous variables are presented as median (range) and for discrete variables as fraction positive (percent).

^b Patients on the renal transplant waiting list between November, 1986 and January, 1987.

^c Patients referred for renal transplantation between February 1987 and June 1990.

^d For prevalent patients, the first serum sample available during the period between November 1986 and January 1987, and for incident patients, the first serum sample available within the first six months of referral for transplantation.

^e Baseline covariates and follow-up until death, loss to follow-up or December 31, 1995, whichever occurred earlier.

significant correlation with the ranked failure times. A graphical check was also made by plotting the residuals against time and fitting a smooth curve with 95% confidence bands. Potential influence points were checked by looking at the score residuals. Linearity of covariates was assessed by modeling the binary outcome in a Poisson generalized additive regression as a function of all the terms in the final survival model using a smoothing spline representation of the continuous variables and an offset term that equaled the difference between the log of the predicted values and the linear predictor from the Cox model. We added 0.01 to those values predicted to equal zero in order to be able to calculate the log.

The model for specific causes of death (liver disease or infection) used the same variables as in the final all-cause mortality model. Because patients were not dialyzed at the transplant centers and patients using the same dialysis unit could have been referred to different transplant centers, we did not include transplant center as a stratification variable in the main analysis. However, we did check that including transplantation center as a stratification factor did not substantially change the results.

Calculations were performed using SAS/Stat version 6.12 (SAS Institute Inc., Cary, NC, USA), except for residual diagnostics which were performed using S-Plus version 3.3 for Windows (StatSci, a division of MathSoft Inc., Seattle, WA, USA).

RESULTS

Prevalence of anti-hepatitis C virus antibody and description of study groups

Sera were available for anti-HCV testing in 394 (60%) of 655 patients in the prevalent population, 1150 (44%) of 2588 patients in the incident population and 1544 (48%) of 3243 patients in the total population (Table 1). One hundred and thirty-nine (35%) of 394 patients in the prevalent population tested positive for anti-HCV compared to 148 (13%) of 1150 patients in the incident population ($P = 0.001$). Thus, overall 287 (19%) of 1544 patients tested positive for anti-HCV. Two hundred and eighty-six randomly selected anti-HCV negative patients served as controls. Thus, a total of 573 patients (261 prevalent and 312 incident patients) were selected for the study.

Complete information on baseline covariates, subsequent transplantation and mortality was available in 217 (84%) of 261 prevalent patients, 279 (90%) of 312 incident patients and 496 (87%) of 573 patients overall. This constituted the final study sample. Median follow-up was 84 months (range 1 to 110) in the

prevalent patients, 70 months (1 to 110) in the incident patients and 73 months (1 to 110 months) overall.

Prevalent and incident cohorts at baseline

As shown in Table 2, the prevalent sample had a higher proportion of patients with ESRD due to glomerular disease, history of previous transplantation, history of blood transfusions, high titers of panel reactive antibodies and history of liver disease, and a lower proportion of patients with diabetes mellitus. Since anti-HCV negative controls were selected separately for the prevalent and incident samples, the two samples were combined for further analyses.

Anti-hepatitis C virus antibody status, transplantation and death

Among the 496 patients in the final study sample, 302 (61%) patients underwent renal transplantation and 154 (31%) patients died (Table 3). The cause of death was ascertained in 133 (86%) of 154 patients who died, and was liver disease in 12 (9%) and infection in 38 (29%). Comparing anti-HCV positive to anti-HCV negative patients, median follow-up was 72 versus 73 months, respectively. The proportion of patients who underwent transplantation was 50% versus 70%, respectively. The all-cause mortality was 38% versus 26%, respectively. Liver disease or infection was the cause of death in 43% versus 30% of deaths, respectively.

Figure 1 shows the survival since start of renal replacement therapy among anti-HCV positive and negative patients (Fig. 1A), and the contribution of patients to the survival curve according to their anti-HCV status and whether they underwent transplantation (Fig. 1B-E). The impact of the left truncation is apparent in Figure 1. Anti-HCV negative patients (Fig. 1B, C) contributed more to the early part of the survival curve than did anti-HCV positive patients (Fig. 1D, E).

Univariate model. The univariate model showed that transplantation had a non-linear effect that depended on the time since transplant. Compared to patients who remained on dialysis, mortality was higher for transplanted patients in the first six months following transplantation, but was lower thereafter. We modeled this as a step function (Table 4) in which the relative risks of death (and 95% confidence intervals) were 4.28 (2.51 to 7.30) in the first three months, 1.51 (0.64 to 3.51) in the next three months, 0.28 (0.15 to 0.49) from seven months to four years, and 0.80 (0.49 to 1.30) after four years. Anti-HCV positive status was associated with a 1.35-fold (0.97 to 1.89) higher risk of death.

Table 2. Clinical characteristics of prevalent and incident patients on the renal transplantation waiting list^a

	Prevalent N = 217 ^b	Incident N = 279 ^c	P ^d
Age years	40 (9–68)	39 (1–76)	0.39
Gender % male	112/217 (52%)	164/279 (59%)	0.11
Race % Caucasian	157/217 (72%)	216/279 (77%)	0.10
Diabetes mellitus	27/217 (12%)	67/279 (24%)	0.001
Time since initiation of renal replacement therapy months	73 (0–245)	15 (0–279)	<0.001
Dialysis modality % hemodialysis	188/212 (87%)	223/267 (84%)	0.11
Number of previous transplants			0.001
0	103/217 (47%)	202/279 (72%)	
1	85/217 (39%)	60/279 (21%)	
2	25/217 (12%)	12/279 (4%)	
3	4/217 (2%)	5/279 (2%)	
Number of transfusions			0.001
0	4/129 (3%)	28/157 (18%)	
1–5	26/129 (20%)	45/157 (29%)	
6–10	21/129 (16%)	28/157 (18%)	
>10	78/129 (61%)	56/157 (35%)	
Blood group			0.40
A	64/192 (33%)	90/236 (38%)	
B	17/192 (9%)	28/236 (12%)	
AB	7/192 (4%)	6/236 (3%)	
O	104/192 (54%)	112/236 (47%)	
Panel reactive antibody %			0.01
<10	11/48 (23%)	62/130 (48%)	
10–50	17/48 (35%)	28/130 (22%)	
50–90	10/48 (21%)	25/130 (19%)	
>90	10/48 (21%)	15/130 (11%)	
Hepatitis B serology			
HBsAg	3/160 (2%)	5/219 (2%)	0.79
Anti-HBs	27/98 (28%)	42/159 (26%)	0.84
Anti-HBc	6/27 (22%)	5/36 (14%)	0.39
Anti-CMV	42/72 (58%)	99/179 (55%)	0.68
History of liver disease	50/201 (25%)	47/271 (17%)	0.05
Elevated ALT ^e	7/122 (6%)	11/159 (7%)	0.81
Albumin g/dl	3.8 (2.2–5.1)	3.9 (2.0–5.1)	0.24

^a Data for continuous variables are presented as median (range) and for discrete variables as fraction positive (percent).

^b Patients on the renal transplant waiting list between November, 1986 and January, 1987.

^c Patients referred for renal transplantation between February, 1987 and June, 1990.

^d Pearson's chi-square test for discrete variables and Student's *t*-test for continuous data.

^e Greater than two and a half times the upper limit of normal.

Examination of the baseline covariates showed that each additional year of age at onset of renal replacement therapy and the diagnosis of diabetes conferred a relative risk of death of 1.05 (1.03 to 1.06) and 1.99 (1.35 to 2.95), respectively. Gender, race and number of previous transplants were not significant predictors of mortality, nor were any of the other variables listed in Table 2.

Final multivariate model. None of the interactions terms tested were significant and hence none were included in the final model. Therefore, the final multivariate model consisted of anti-HCV status at baseline, transplantation, age and diabetes (Table 4). Comparing anti-HCV positive patients to anti-HCV negative patients, the relative risk of death from all causes was 1.41 (1.01 to 1.97) and the relative risk of death due to liver disease or infection was 2.39 (1.28 to 4.48). Comparing patients who underwent

transplantation to those who remained on dialysis, the relative risk of death from all causes between 0 to 3 months, 3 to 6 months, seven months-four years and after four years was 4.75 (2.76 to 8.17), 1.76 (0.75 to 4.13), 0.31 (0.18 to 0.54) and 0.84 (0.51 to 1.37), respectively. There was no interaction between the effect of anti-HCV status at baseline and subsequent transplantation ($P = 0.93$), meaning that the association of these two variables with survival was independent of each other. The absence of interaction is shown in Figure 2, where the relative risk of death among patients who underwent transplantation compared to those who remained on dialysis was similar among anti-HCV positive and negative patients, at all intervals after transplantation. For each additional year of age at onset of renal replacement therapy and the diagnosis of diabetes the relative risk of death was 1.05 (1.03 to 1.06) and 1.75 (1.19 to 2.59), respectively. Inclusion of transplant center as a stratification variable in the regression model did not affect the regression coefficients significantly. The point estimate for the relative risk of death for anti-HCV was 1.36 and for transplantation was 4.68, 1.64, 0.34 and 0.93, respectively between 0 to 3 months, 3 to 6 months, 7 months to 4 years and after 4 years. Residual diagnostics showed no evidence of nonlinearity, lack of proportional hazards or the presence of any influence points.

DISCUSSION

This study demonstrates that among patients referred for renal transplantation to the 14 transplant centers served by the New England Organ Bank between 1986 and 1990, the presence of anti-HCV was associated with a higher risk of death. Receiving a transplant was associated with a higher risk of death within the first six months after surgery, but a lower risk of death thereafter. Most important, these two associations were independent, indicating that the presence of anti-HCV is associated with a poor prognosis, irrespective of whether the patient receives a transplant or remains on dialysis, and that the effect of transplantation was similar in anti-HCV positive and negative patients referred for transplantation. These findings have important implications for policies in dialysis units and transplant programs.

In designing this study, two potential causes of bias in patient selection had to be taken into account. First, physicians' decisions to refer patients for transplantation could have been influenced by their knowledge of the patients' anti-HCV status. To avoid this bias, we only included patients who were referred for renal transplantation prior to the advent of anti-HCV testing in June 1990. Second, physicians tend to refer healthier patients for transplantation, leaving sicker patients on dialysis. Indeed, crude mortality rates among dialysis patients are twice as high in patients who are not referred for renal transplantation compared to patients who are referred for transplantation [11]. To avoid this bias, we only included patients who completed the requisite pre-transplantation medical evaluation process, were deemed suitable transplant candidates by their treating physician, and were placed on the waiting list. Nonetheless, the possibility cannot be excluded that medical contraindications for renal transplantation arising after listing may have precluded renal transplantation in some patients, thus contributing to the increased risk of death in the dialysis group.

Using ELISA3, we found a 19% prevalence of anti-HCV among dialysis patients referred for renal transplantation. As discussed earlier, these results are similar to those in other dialysis

Table 3. Subsequent transplantation and mortality among anti-HCV positive and negative patients referred for renal transplantation^a

Anti-HCV ^b	Follow-up months	Subsequent transplantation ^c	All-cause mortality ^c	Cause of death ascertained	Deaths from liver disease ^d	Deaths from infection ^d	Deaths from liver disease or infection ^d
Positive (N = 223)	72 (1–108)	111 (50%)	84 (38%)	76 (90%)	11 (14%)	22 (29%)	33 (43%)
Negative (N = 273)	73 (1–110)	191 (70%)	70 (26%)	57 (81%)	1 (2%)	16 (28%)	17 (30%)
Overall (N = 496)	73 (1–110)	302 (61%)	154 (31%)	133 (86%)	12 (9%)	38 (29%)	50 (38%)

^a Data for continuous variables are presented as median (range) and for discrete variables as fraction positive (percent).

^b In the first serum sample available during the period between November 1986 and January 1987 (prevalent patients) or the first serum sample available within the first six months of referral for transplantation (incident patients).

^c Follow-up until death, loss to follow-up or December 31, 1995, whichever occurred earlier.

^d Among those in whom the cause of death was ascertained.

centers in the U.S. [2]. The 35% prevalence of anti-HCV among patients on the renal transplant waiting list in 1986 (prevalent population) was significantly higher than the 13% prevalence among patients referred for renal transplantation between 1987 and 1990 (incident population). The higher prevalence of anti-HCV in the prevalent population was probably due to the fact that this group had a higher proportion of highly sensitized patients, who had been on the waiting list longer and had received multiple blood transfusions or previous kidney transplants. These factors are all associated with a higher risk of acquiring HCV infection. The lower prevalence of anti-HCV among patients referred for renal transplantation after 1987 may also reflect a declining trend in the incidence and prevalence of non-A, non-B hepatitis (NANBH) that was observed even prior to the discovery of HCV [2]. This decline was probably the result of exclusion of blood products that tested positive for surrogate markers of NANBH such as elevated ALT and anti-HBc, and the implementation of strategies to reduce transmission of blood-borne infections in dialysis units [16, 17]. Since the discovery of HCV, the advent of testing of blood products for anti-HCV and the implementation of even more rigorous infection-control measures have led to a further decline in the incidence and prevalence of HCV infection. Overall, the incidence of NANBH among dialysis patients in the U.S. declined from 1.7% in 1982 to 0.5% in 1992 [2].

Among patients referred for renal transplantation, the presence of HCV infection was associated with a 1.41-fold (1.01- to 1.97-fold) increased risk of death. These findings confirm previous studies from our group [3] and others [10] showing that pre-transplantation HCV infection is associated with an increased mortality after transplantation. In a randomly selected cohort of 103 patients who received kidneys from anti-HCV negative donors at NEOB transplant centers between 1986 and 1990, recipients with pre-transplantation anti-HCV had a 3.3-fold higher risk of death than recipients without pre-transplantation anti-HCV [3]. The lower relative risk of death for anti-HCV positive patients in the current study (1.4) compared to our previous results (3.3) appears to be the result of a higher mortality among anti-HCV negative patients in the current study (26%) compared to our previous study (15%). One possible explanation for this finding is that some of the anti-HCV negative patients in the current study may have acquired the HCV infection during the interval between referral for transplantation and receiving the transplant. Evaluation of this hypothesis would require testing of serial serum specimens.

In contrast, others have not detected significant differences in patient survival between transplant recipients with and without

pre-transplantation anti-HCV [4, 7, 9]. The different results among studies could be due to factors such as differences in selection of patients and more importantly, the limited duration and completeness of follow-up in studies that did not find an increased risk of death among anti-HCV positive patients. Indeed, the progression of liver disease due to HCV and its attendant complications are related to the duration of infection. The interval between the initial presentation of post-transfusion NANBH and the onset of chronic hepatitis, cirrhosis and hepatocellular carcinoma is 10, 21 and 29 years, respectively [18]. We rigorously tracked post-transplantation outcomes in all patients. Similar results were not reported in the studies by others. In principle, a less complete follow-up could possibly fail to identify patients who died. Alternatively, this difference might reflect differences in the severity of HCV infection. In our study, 40% of anti-HCV positive patients had a history of liver disease at the time of referral for transplantation (data not shown). Indeed, pre-transplantation liver disease is associated with an increased risk of death [3]. In principle, a lower prevalence of pre-transplantation liver disease among anti-HCV positive recipients in other studies would be reflected in a higher post-transplantation survival! More accurate assessment of the severity of pre-transplantation liver disease, for example liver biopsy, would be necessary to address this question. Indeed, pre-transplantation liver histology has been shown to be a good predictor of adverse post-transplantation outcomes [19]. Finally, the virulence of the virus differs between strains of the virus, and the differences in the distribution of various strains could possibly explain differences in the results obtained from different geographical regions.

Our finding of an increased mortality among anti-HCV positive ESRD patients referred for renal transplantation is at variance with outcomes in some studies on non-ESRD patients with post-transfusion NANBH. Seeff and colleagues studied long-term outcomes in five studies of transfusion-associated hepatitis that began between 1967 and 1980 [20]. After an average of 18 years of follow-up, the overall mortality was 51% among patients with post-transfusion NANBH as well as in two control groups of patients who had received transfusions but had not developed NANBH. Since HCV accounts for more than 60% of NANBH, these results suggest that post-transfusion HCV infection did not adversely affect survival, at least for up to two decades. Possibly the greater adverse effect of HCV infection in patients with ESRD is the result of immune dysfunction. Indeed, patients with ESRD are afflicted by several defects in cellular and humoral mechanisms including abnormal chemotaxis, adherence, phagocytosis and release of mediators by granulocytes, impaired function

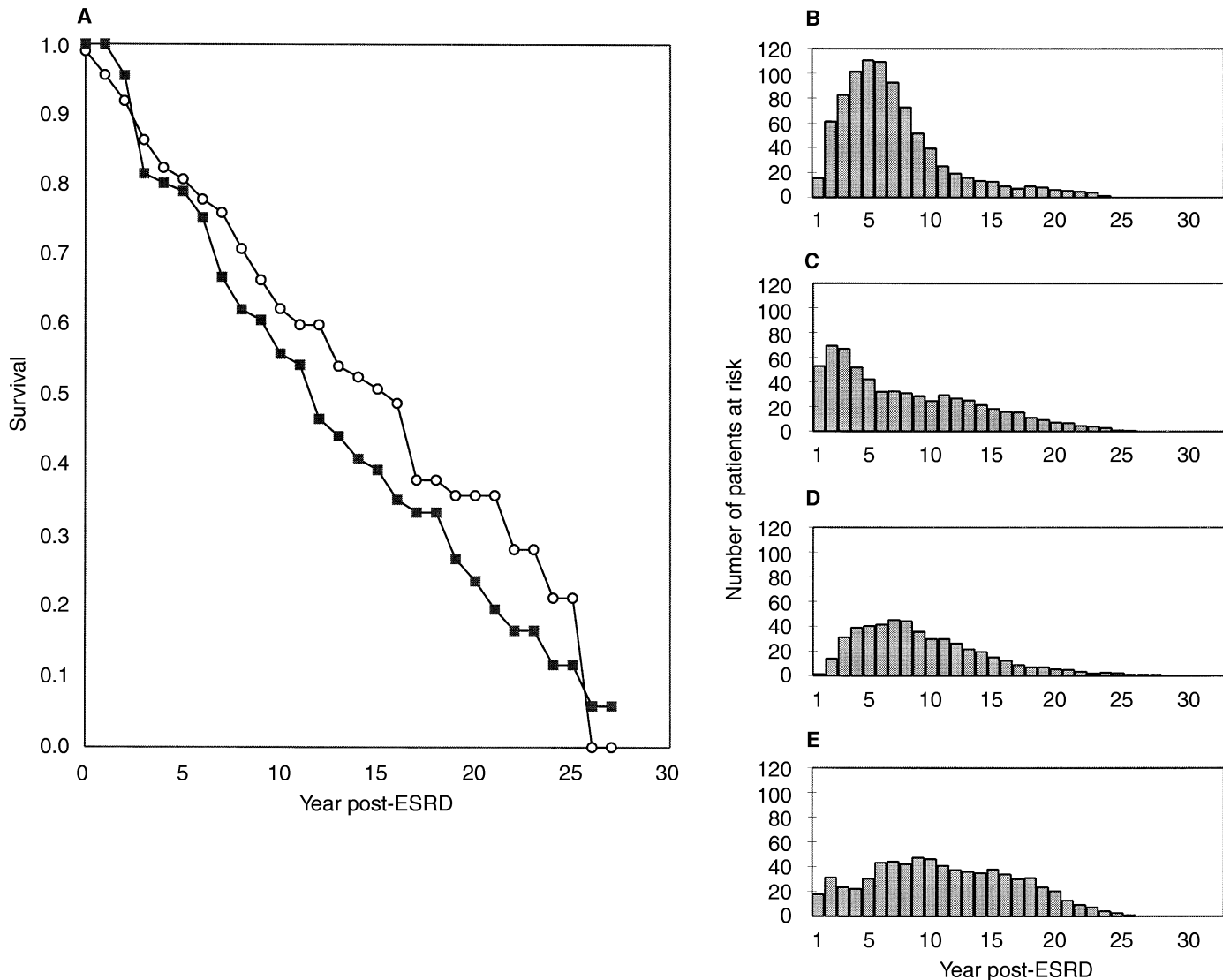


Fig. 1. Survival among anti-HCV negative and positive patients referred for renal transplantation. (A) The unadjusted actuarial survival from the time of first initiation of renal replacement therapy (dialysis or transplantation) until death, loss to follow-up or December 31, 1995, whichever occurred first. Symbols are: (○) anti-HCV negative; (■) anti-HCV positive. (B through E) The number of anti-HCV negative and positive patients contributing to different parts of the survival curve as either dialysis or transplant patients. Anti-HCV negative patients (B, transplant; C, dialysis) contributed more to the early part of the survival curve than did anti-HCV positive patients (D, transplant; E, dialysis). A higher proportion of anti-HCV negative patients (B, C) underwent transplantation than did anti-HCV positive patients (D, E).

of macrophage Fc receptors [21], and defective T- lymphocyte function [22].

Patients with advanced liver disease in general and cirrhosis in particular have multiple immunological defects including reduced cell-mediated immunity [23, 24]; reduced neutrophil phagocytic and killing ability [25] and impaired macrophage Fc receptor function [26]. The immune dysfunction due to liver disease is likely to be exacerbated by the immune dysfunction of uremia and consequently increase the susceptibility to lethal infections. Therefore, we also included death due to liver disease or infection as an end-point. In the current study, we observed a 2.4-fold higher risk of death due to liver disease or infection among anti-HCV positive patients referred for renal transplantation. An increased risk of death due to liver disease among anti-HCV

positive patients has also been observed in non-ESRD patients. Among patients with post-transfusion NANBH, Seeff and colleague observed that the frequency of death due to liver disease was 3.3% compared to 1.1% and 2.0% in two control cohorts without NANBH [20]. Deaths due to infection were not reported in this study.

The higher mortality in ESRD patients with anti-HCV underscores the importance in preventing HCV infection in these patients. These patients are at risk of acquiring HCV infection from blood product transfusions or from other patients in hemodialysis units. The advent of screening of blood products for anti-HCV in 1990 has virtually eliminated the transmission of HCV infection by blood product transfusions[27]. Nonetheless, factors responsible for nosocomial transmission within dialysis

Table 4. Relative risk of death among patients referred for renal transplantation^a

Risk factor	Relative risk of death (95% confidence intervals)		
	Univariate model all-cause mortality	Final multivariate model	
		All cause mortality	Mortality due to liver disease or infection
Anti-HCV positive (vs. negative) ^b	1.35 (0.97–1.89)	1.41 (1.01–1.97)	2.39 (1.28–4.48)
Transplantation (vs. dialysis)	Overall $P < 0.0001$	Overall $P < 0.0001$	Overall $P < 0.0001$
0–3 months post-transplantation	4.28 (2.51–7.30)	4.75 (2.76–8.17)	11.44 (5.33–24.55)
4–6 months post-transplantation	1.51 (0.64–3.51)	1.76 (0.75–4.13)	4.10 (1.33–12.67)
7–47 months post-transplantation	0.28 (0.15–0.49)	0.31 (0.18–0.54)	0.37 (0.13–1.08)
>48 months post-transplantation	0.80 (0.49–1.30)	0.84 (0.51–1.37)	0.67 (0.22–2.00)
Age at onset of ESRD (per year)	1.05 (1.03–1.06)	1.05 (1.03–1.06)	1.05 (1.03–1.08)
Diabetes mellitus (vs. non-diabetics)	1.99 (1.35–2.95)	1.75 (1.19–2.59)	1.15 (0.55–2.40)
Number of previous transplants	1.02 (0.79–1.31)		
Female gender (vs. male)	0.79 (0.57–1.09)		
Non-white race (vs. white)	1.28 (0.90–1.81)		

^a Patients on the renal transplant waiting list between November 1986 and January 1987 (prevalent patients), and those referred for renal transplantation between February 1987 and June 1990 (incident patients).

^b In the first serum sample available during the period between November 1986 and January 1987 (prevalent patients) or the first serum sample available within the first six months of referral for transplantation (incident patients).

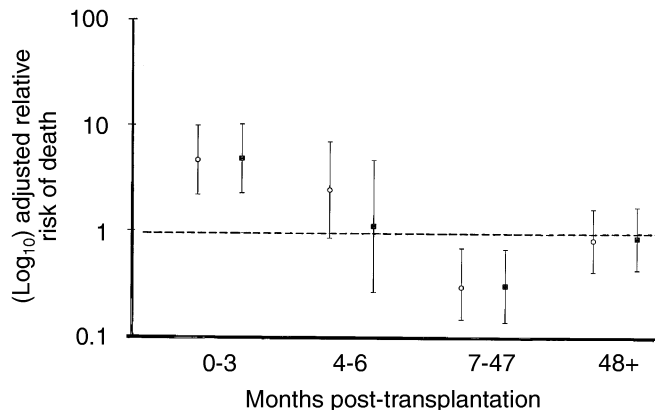


Fig. 2. Relative risk of death for transplantation versus dialysis among anti-HCV negative (○) and positive (■) patients referred for renal transplantation. The relative risk of death (and 95% confidence intervals) for different time intervals after transplantation are adjusted for age and the presence of diabetes. The relative risk of death for transplantation versus dialysis was similar for anti-HCV positive and negative patients at all intervals after transplantation.

units are not well understood [1]. We recommend continuing study of methods for control of HCV infection in dialysis units.

This study also demonstrates a long-term beneficial effect of transplantation on survival of patients with ESRD. We observed an initially higher risk of death (relative risk of 4.75 and 1.76 between 0 to 3 months and 3 to 6 months, respectively), but a lower risk thereafter (0.31 between 7 months and 4 years, and 0.84 after 4 years). These findings are similar to those reported by Port and colleagues using a similar study design [11]. Compared to wait-listed dialysis patients, Port and colleagues observed a higher relative risk of death in the first month after cadaveric renal transplant (relative risk of 2.43), but a lower risk thereafter (relative risk 0.96 between 1 to 12 months and 0.36 after 12 months). The absence of a significant interaction between anti-HCV status and transplantation in our study indicates that the effect of transplantation on survival was similar in anti-HCV positive and negative patients (Fig. 2). These findings are con-

sistent with those of a recent study by Knoll and colleagues who compared clinical outcomes among anti-HCV positive patients referred for renal transplantation [28]. They found that patient survival was significantly higher among the 33 patients who underwent transplantation compared to the 25 patients who remained on dialysis.

For several reasons, it has been assumed that the immunosuppression regimens used for renal transplantation may worsen the course of HCV infection in ESRD. First, a higher prevalence of chronic liver disease, overall mortality and death due to liver disease has been reported among HBsAg positive patients who underwent renal transplantation compared to those who remained on dialysis [12, 29]. Second, among patients with HIV infection, the acquired immunodeficiency syndrome (AIDS) develops 1.5 to 2 years after infection in immunosuppressed transplant recipients, compared to 7 to 8 years after infection in normal hosts [13]. Third, among anti-HCV positive transplant recipients, liver disease is seen more often among those who receive antilymphocyte preparations such as antilymphocyte globulin, antithymocyte globulin or OKT3 than those who do not [30, 31]. Fourth, among patients with HCV infection at the time of transplantation, we have previously reported a median 6.6-fold increase in HCV RNA titers after transplantation [3]. Finally, in patients with primary hypogammaglobulinemia, HCV infection appears to have an accelerated course. In one study [32], 73% developed chronic active hepatitis and/or cirrhosis within a decade after acquiring HCV infection. Overall, these observations support the hypothesis that immunosuppressed patients are more likely to develop adverse consequences of viral infections. Consequently, transplant physicians have been reluctant to offer anti-HCV positive ESRD patients the choice of renal transplantation. Nonetheless, we found that the association between transplantation and survival was no different between anti-HCV positive and negative patients. Thus, the possible detrimental effect of transplantation on the course of HCV infection does not appear to outweigh its long-term beneficial effect on survival in ESRD. Hence, our results do not support withholding renal transplantation solely on the basis of a positive anti-HCV test.

In conclusion, HCV infection at the time of transplantation is

associated with an increased risk of death, irrespective of whether patients remain on dialysis or undergo transplantation. These results emphasize the importance of measures to prevent nosocomial transmission of HCV in dialysis units. In the absence of a prospective randomized trial, definitive conclusions cannot be drawn regarding the risk of death among anti-HCV positive ESRD patients treated by transplantation compared to dialysis. Our study suggests that transplantation has a beneficial rather than adverse effect on long-term survival in anti-HCV positive patients. Hence, anti-HCV positive status alone is not a contraindication for renal transplantation, and anti-HCV positive ESRD patients should be allowed to make an informed choice between dialysis or transplantation.

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